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Faecal haemoglobin distributions by sex, age, deprivation and geographical region: consequences for colorectal cancer screening strategies.

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Abbreviations

BoSS; Bowel Screening Scotland, CRC; colorectal cancer, FFLT; FIT as a first-line test: FIT; faecal immunochemical test for haemoglobin; f-Hb; faecal haemoglobin concentration; GP, general practitioner, gFOBT, guaiac faecal occult blood test: Hb; haemoglobin, ISD; Information Services Division, ISO: International Organization for Standardization, NHS; National Health Service, NSS; National Services Scotland, SBoSL; Scottish Bowel Screening Laboratory, SBoSP; Scottish Bowel Screening Programme, SBoSP TA&A: SBoSP in NHS Tayside and NHS Ayrshire and Arran, SIMD; Scottish Index of Multiple Deprivation, UK; United Kingdom

Abstract

Background: Faecal immunochemical tests for haemoglobin (FIT) are becoming widely used in colorectal cancer screening and assessment of symptomatic patients. Faecal haemoglobin concentration (f-Hb) thresholds are used to guide subsequent investigation. We established the distributions of f-Hb in a large screening population by sex, age, deprivation and geography.

Methods: Single estimates of f-Hb were documented for all individuals participating in the first 18 months of the Scottish Bowel Screening Programme (SBoSP). The distributions of f-Hb were generated for all participants, all men and women, and men and woman by age quintile and deprivation quintile. Distributions were also generated by geographical region for all participants, men and women, and by deprivation. Comparisons of f-Hb distributions with those found in a pilot evaluation of FIT and three other countries were performed.

Results: f-Hb was documented for 887,248 screening participants, 422,385 men and 464,863 women. f-Hb varied by sex, age, deprivation quintile and geographical region. The f-Hb distributions by sex and age differed between the SBoSP and the pilot evaluation and the three other countries.

Conclusions: f-Hb is higher in men than women and increases with age and deprivation in both sexes. f-Hb also varies by geographical region, independently of deprivation, and by country. The f-Hb distribution estimated by pilot evaluation may not represent the population distribution. Decision limits have advantages over

reference intervals. Use of partitioned f-Hb thresholds for further investigation, based on the data generated, have advantages and disadvantages, as do risk scores based on a spectrum of influencing variables.

Introduction

Colorectal cancer (CRC) incidence and mortality rates vary markedly from country to country but, globally, CRC is the third most commonly diagnosed cancer in men and the second in women, with 1.8 million new cases and almost 861,000 deaths in 2018, according to the World Health Organization. (1) However, early detection can be achieved using quantitative faecal immunochemical tests for haemoglobin (FIT), which measure faecal haemoglobin concentration (f-Hb), leading to better outcomes for individuals. FIT can be used in asymptomatic population screening, (2) in assessment of patients presenting with lower bowel symptoms, (3) and in adenoma surveillance programmes. (4) In general, in all these clinical settings, a single f-Hb threshold is set to decide which individuals should be invited for further investigation, usually colonoscopy. The threshold applied varies according to the clinical setting and differs considerably from country to country, and even from region to region in a country.

In asymptomatic population-based screening, only one f-Hb threshold is generally used in any programme, such as 80 μg Hb/g faeces in the Scottish Bowel Screening Programme (SBoSP), although this has been widely criticised. We have shown that f-Hb is higher in men than women and rises with age and have documented the effect of these variables on screening programme positivity and future risk of colorectal neoplasia. (5) We have also suggested that, while f-Hb was higher in men than women and rose with age in Taiwan, Florence and Barcelona, (6,7) as well as in Scotland, the data are not transferrable over geography. Further, we have shown that f-Hb increases with socio-economic deprivation. (8) These findings have been confirmed in studies from South Australia (9) and England. (10) In addition, other variables affect f-Hb; for example, f-Hb is higher in prevalence than in incidence screening. (11) Further, pre-analytical and analytical variables, including specimen temperature and collection device buffer formulation, affect f-Hb. (12)

In consequence, there have been several studies, recently reviewed, concerning the use of different thresholds for men and women and for different age groups to enhance the equality of outcomes for all individuals. (13) Most studies to date conclude that further work is needed, for example, Brenner *et al* (14) state that: “there are major differences in diagnostic performance parameters according to sex and age, which should receive careful attention in the interpretation and comparison of results of FIT-based CRC screening studies.” Rather than simply using different thresholds according to sex and age, a strategy that is now creating significant interest is the creation and application of risk scores, mathematical algorithms based on variables known to affect CRC incidence, including sex, age, deprivation and many other possible variables. A recent review described published risk scores for colorectal neoplasia and identified 87 variables (excluding major genetic variants and single nucleotide polymorphisms) that had been applied across all studies examined: a few include f-Hb. (15)

Scotland began CRC screening in 2000 with three pilot screening rounds based upon use of guaiac-based faecal occult blood tests (gFOBT). (16) The first fully rolled out national CRC screening programme in the world then commenced in 2007 with a two-tier reflex gFOBT/qualitative FIT strategy. (17) It became abundantly clear that FIT had many advantages over gFOBT (2) and a pilot evaluation of FIT as a first-line test (FFLT) was conducted in 2010. (18) In November 2017, the SBoSP evolved to use quantitative FIT as the primary screening test. (19)

We have here generated the f-Hb distributions by sex, age, deprivation in detail and, for the first time, geographical region, derived from the data generated from a screening population of almost one million participants. We have examined the implications for screening, reference values, the use of stratified f-Hb thresholds and the creation and application of risk scores. We also assessed whether the data on f-Hb from the FFLT pilot evaluation (5,8) informed or confounded the decision made on the threshold set in the SBoSP and compared f-Hb distributions from both SBoSP and FFLT with published data from other countries. (6,7)

Methods

The details of the SBoSP have been documented previously. (16,17) Regular updates on the key performance indicators are published and available on the Internet. (20) In brief, in the FIT-based SBoSP, one FIT specimen collection device (Hitachi Chemical Diagnostic Systems Co., Ltd, Tokyo, Japan) is sent in the post every two years to all men and women registered with a General Practitioner (GP) and aged between 50 and 74 years, with older age opt-in, along with information on the SBoSP, instructions on how to collect and handle the sample and a pre-paid envelope for return of the device to the Scottish Bowel Screening Laboratory (SBoSL). Evaluable devices returned are analysed on one of four HM-JACKarc FIT systems (Hitachi Chemical Diagnostic Systems Co., Ltd) in the SBoSL, which has International Organization for Standardization (ISO) 15189 accreditation. Total quality management is comprehensively practiced, including internal quality control and external quality assessment carried out by the UK National External Quality Assessment Scheme. Data from every participant on f-Hb, sex, age in quintiles, degree of deprivation in quintiles and National Health Service (NHS) Board of residence were available from the Bowel Screening Scotland (BoSS) system. Deprivation was assessed using the Scottish Index of Multiple Deprivation (SIMD), a measure of the extent to which an area is deprived across seven domains: income, employment, education, health, access to services, crime and housing. (21) The centiles of f-Hb distributions from the data in the first 18 months of the FIT-based SBoSP (November 2017 to April 2018) were created by the Information Services Division (ISD) of National Services Scotland (NSS).

As described in detail previously, (18) the FFLT evaluation was carried out in two NHS Boards (Tayside, and Ayrshire and Arran) in 2010; every eligible person was sent a specimen collection device for the OC-Sensor Diana (Eiken Chemical Co., Ltd, Tokyo, Japan), along with information on how to perform the test and on the SBoSP, along with a return envelope. Analysis was performed on one of two OC-Sensor Diana FIT systems (Eiken Chemical Co., Ltd, Tokyo, Japan) in the SBoSL. Data on f-Hb centiles by age and sex from the FFLT were compared to those in the SBoSP to investigate to what extent the pilot evaluation had informed, or confounded, the subsequent performance of the SBoSP in the whole population and were also compared to previously published data from three other countries. (6,7) R statistical software version 3.2.3 was used for all calculations of centiles in f-Hb distributions.

Results

The 90th, 95th and 97.5th centiles for all 887,248 participants in the first 18 months of the FIT-based SBoSP are shown in Table 1. The centiles documented are those for which the f-Hb was greater than the limit of detection of the FIT system used, 2 µg Hb/g faeces, since f-Hb lower than this are indistinguishable from samples with no Hb. (22) The 95th centiles of f-Hb in all participants by sex, and by sex and age quintile (years), are shown in Figure 1. As in previous studies, (5-7,9,10), overall the 422,385 men had higher f-Hb than the 464,863 women. Further, when grouped by age quintile, 50-54, 55-59, 60-64, 65-69 and 70 years or more, f-Hb rose with age in both men and women.

Table 1. Centiles of distribution of faecal haemoglobin concentration (µg Hb/g faeces) for all participants, all men and women, and all men and all women by age quintile (years).

Age (years)	Sex	SIMD	n	Centile 90th	Centile 95th	Centile 97.5th
All	All	All	887,248	13.6	40.2	105.4
All	Men	All	422,385	17.5	49.9	136.1
All	Women	All	464,863	10.5	32.2	82.5
50-54	Men	All	105,861	9.3	30.1	83.4
55-59	Men	All	77,312	12.9	39.0	104.6
60-64	Men	All	98,442	18.3	50.5	140.9
65-69	Men	All	68,073	23.8	64.9	179.3
70+	Men	All	72,697	29.4	77.6	216.1

50-54	Women	All	116,406	6.2	21.2	60.5
55-59	Women	All	85,044	7.8	25.8	69.9
60-64	Women	All	108,357	10.5	31.3	80.0
65-69	Women	All	73,858	13.7	39.6	98.2
70+	Women	All	81,198	17.7	47.6	116.8

The 90th, 95th and 97.5th centiles of f-Hb, grouped by sex and SIMD quintile, and age are shown in Table 2. The 95th centiles of f-Hb in men by age quintile (years) and Scottish Index of Multiple Deprivation (SIMD) quintile are shown in Figure 2: women show a similar pattern but with lower f-Hb. Once again, f-Hb is higher in men than women and rises with age; the new data here confirm, in much more detail than previously published (8,9), that f-Hb rises with deprivation. Further, f-Hb rises with increasing deprivation in both men and women and throughout the age gradient.

Table 2. Centiles of distribution of faecal haemoglobin concentration (µg Hb/g faeces) for all men and women by age quintile (years) and by increasing deprivation by Scottish Index of Multiple Morbidity (SIMD): 5 = least deprived: 1 = most deprived.

Age (years)	Sex	SIMD	n	Centile 90th	Centile 95th	Centile 97.5th
50-54	Men	5	23,814	6.0	20.1	59.3
50-54	Men	4	23,843	7.5	25.3	70.0
50-54	Men	3	21,613	8.7	26.8	72.5
50-54	Men	2	19,275	11.0	37.3	99.9
50-54	Men	1	17,204	16.3	51.2	155.7
55-59	Men	5	17,060	8.5	25.9	72.3
55-59	Men	4	17,589	10.1	29.1	87.2
55-59	Men	3	16,085	12.1	35.9	88.2
55-59	Men	2	14,036	15.8	46.4	125.2

55-59	Men	1	12,468	23.1	68.1	190.6
60-64	Men	5	22,510	13.1	38.2	101.2
60-64	Men	4	22,470	14.4	39.7	101.8
60-64	Men	3	20,736	18.2	52.1	146.3
60-64	Men	2	17,958	23.4	61.0	181.7
60-64	Men	1	14,686	27.8	78.8	234.7
65-69	Men	5	15,797	16.8	47.0	120.6
65-69	Men	4	16,014	19.6	54.1	148.4
65-69	Men	3	14,406	23.2	65.6	192.1
65-69	Men	2	12,249	30.5	85.5	243.0
65-69	Men	1	9,567	36.7	97.2	263.1
70+	Men	5	17,059	22.3	62.3	162.3
70+	Men	4	17,147	24.5	67.7	175.4
70+	Men	3	15,827	29.1	76.5	199.0
70+	Men	2	13,034	34.9	88.1	259.8
70+	Male	1	9,582	42.6	123.1	389.4
50-54	Women	5	26,828	4.1	14.9	43.0
50-54	Women	4	26,362	5.0	16.9	47.1
50-54	Women	3	24,146	5.7	19.3	54.7
50-54	Women	2	20,902	7.7	25.7	74.1
50-54	Women	1	18,087	11.7	39.5	101.2
55-59	Women	5	18,979	4.9	17.0	48.9
55-59	Women	4	19,670	6.0	20.0	55.8
55-59	Women	3	18,137	7.6	23.4	66.6
55-59	Women	2	15,355	10.3	32.3	87.7
55-59	Women	1	12,848	14.2	42.7	116.6
60-64	Women	5	25,356	6.9	21.2	50.7
60-64	Women	4	24,775	8.4	25.4	61.2
60-64	Women	3	22,782	10.5	31.3	82.2
60-64	Women	2	19,857	13.4	37.4	100.2
60-64	Women	1	15,527	19.2	54.3	131.6
65-69	Women	5	17,222	9.1	28.3	74.6
65-69	Women	4	17,393	11.3	34.2	89.2
65-69	Women	3	15,589	13.6	38.6	93.6
65-69	Women	2	13,430	17.0	45.4	113.2
65-69	Women	1	10,182	23.4	63.1	151.4
70+	Women	5	18,949	13.5	36.9	87.2
70+	Women	4	18,656	13.5	38.7	89.1

70+	Women	3	17,545	17.0	46.4	109.5
70+	Women	2	14,980	20.8	56.1	148.6
70+	Women	1	11,036	30.6	71.8	207.3

The 90th, 95th and 97.5th centiles of distribution of f-Hb for all men and women in four age groups (years) for the FIT-based Scottish Bowel Screening Programme in the two pilot evaluation NHS Boards, NHS Tayside and NHS Ayrshire and Arran (SBoSP TA&A), in the FIT as a first-line test pilot evaluation (FFLT) and in Taiwan, Florence and Barcelona are shown in Table 3. The 95th centiles of f-Hb in men in these cohorts in four age groups (years) are shown in Figure 3: women show a similar pattern but with lower f-Hb. The differences between the f-Hb from the FIT-based SBoSP and the FFLT evaluation are striking, the f-Hb being higher in both men and women in all age groups in the same two NHS Boards in the SBoSP and FFLT. The data on the f-Hb distributions from the FIT-based SBoSP also differ from those from the three other countries, (5,6) confirming that, while f-Hb is higher in men than in women in all age groups, and rises with age in all countries investigated, Scotland remains different to other countries.

Table 3. Centiles of distribution of faecal haemoglobin concentration (µg Hb/g faeces) for all men and women in four age groups (years) for two NHS Boards in the FIT-based Scottish Bowel Screening Programme, NHS Tayside and NHS Ayrshire and Arran (SBoSP TA&A), FIT as a first-line test pilot evaluation (FFLT), and Taiwan, Florence and Barcelona.

Age (years)	Sex	Data source	n	Centile 90th	Centile 95th	Centile 97.5th
50-54	Men	SBoSP TA&A	15,332	9.2	28.0	78.6
55-59	Men	SBoSP TA&A	10,625	12.6	35.7	101.5
60-64	Men	SBoSP TA&A	15,851	18.1	48.9	134.9
65-69	Men	SBoSP TA&A	11,287	22.5	57.6	179.6
50-54	Men	FFLT	4,075	7.0	20.8	56.2
55-59	Men	FFLT	4,160	9.6	30.8	83.0
60-64	Men	FFLT	3,489	12.4	37.0	104.0
65-69	Men	FFLT	3,497	19.6	50.6	142.6
50-54	Men	Taiwan	11,321	7.2	17.2	42.8
55-59	Men	Taiwan	9,769	9.2	22.6	68.4
60-64	Men	Taiwan	8,719	12.6	29.4	81.0
65-69	Men	Taiwan	10,150	15.4	37.8	99.0
50-54	Men	Florence	793	4.4	10.4	32.8
55-59	Men	Florence	1,093	3.6	11.0	23.2
60-64	Men	Florence	1,105	8.8	21.2	77.0
65-69	Men	Florence	1,094	5.6	16.4	55.4
50-54	Men	Barcelona	9,465	7.2	27.2	93.0
55-59	Men	Barcelona	7,834	11.4	48.0	157.2
60-64	Men	Barcelona	8,024	19.2	69.4	195.8
65-69	Male	Barcelona	6,311	22.2	81.0	259.8
50-54	Women	SBoSP TA&A	16,898	6.1	20.9	60.7
55-59	Women	SBoSP TA&A	12,087	7.5	26.8	67.6
60-64	Women	SBoSP TA&A	17,706	10.0	31.0	84.8
65-69	Women	SBoSP TA&A	12,405	12.8	36.7	90.5
50-54	Women	FFLT	4,543	4.6	13.6	34.0
55-59	Women	FFLT	4,730	6.2	18.4	48.8
60-64	Women	FFLT	4,058	6.8	20.2	47.0
65-69	Women	FFLT	3,985	9.0	25.8	63.4
50-54	Women	Taiwan	18,476	6.8	14.4	27.4
55-59	Women	Taiwan	13,959	7.2	15.8	28.4
60-64	Women	Taiwan	12,350	9.4	18.8	39.2
65-69	Women	Taiwan	12,444	11.0	22.8	50.4
50-54	Women	Florence	1,031	3.4	6.4	14.6
55-59	Women	Florence	1,272	3.4	8.4	17.8
60-64	Women	Florence	1,241	3.6	8.8	20.8

65-69	Women	Florence	1,188	5.2	15.0	44.0
50-54	Women	Barcelona	11,520	3.4	11.2	34.6
55-59	Women	Barcelona	9,922	4.8	19.0	55.0
60-64	Women	Barcelona	10,076	7.2	28.0	86.8
65-69	Women	Barcelona	7,623	9.2	28.4	76.2

We explored whether geographical region in Scotland affected f-Hb generating data based upon all 14 NHS Boards responsible for the protection and the improvement of their population's health and for the delivery of frontline healthcare services. The 90th, 95th and 97.5th centiles are shown in Table 4 for all participants and for men and women. Again, men have higher f-Hb than women; importantly, there are clear differences between geographical regions. Since this might well be due to socio-economic factors, we explored the centiles of f-Hb for the 11 mainland NHS Boards in Scotland by SIMD quintile: these data are shown in Supplementary Table 1, which documents that there are differences across geographical regions.

Table 4. Centiles of distribution of faecal haemoglobin concentration for all participants and all men and women in four age groups (years) by geographical region (NHS Board) in Scotland.

Sex	Geographical region by NHS Board	n	Centile 90th	Centile 95th	Centile 97.5th
All	Ayrshire and Arran	66,248	14.7	41.1	114.1
All	Borders	24,528	10.6	33.2	83.2
All	Dumfries and Galloway	29,734	11.0	34.2	85.3
All	Fife	62,878	12.2	37.5	96.9
All	Forth Valley	52,042	12.9	37.8	103.7
All	Grampian	96,914	12.5	37.9	101.7
All	Greater Glasgow and Clyde	168,886	16.5	47.4	123.2
All	Highland	64,212	12.9	38.7	99.7
All	Lanarkshire	104,353	16.7	46.5	124.6
All	Lothian	132,391	11.6	35.4	93.3

All	Orkney	4,213	9.0	25.2	60.2
All	Shetland	4,408	13.5	39.3	103.6
All	Tayside	71,368	12.1	36.5	92.9
All	Western Isles	5,073	18.0	48.6	123.1
Men	Ayrshire and Arran	31,122	19.2	51.3	145.1
Men	Borders	11,647	13.6	40.7	91.9
Men	Dumfries and Galloway	14,040	14.1	39.2	101.4
Men	Fife	29,990	16.0	48.3	126.7
Men	Forth Valley	24,784	16.1	47.1	130.4
Men	Grampian	46,980	15.7	46.4	127.9
Men	Greater Glasgow and Clyde	80,054	20.6	58.9	167.2
Men	Highland	30,800	18.0	50.8	136.2
Men	Lanarkshire	49,531	21.3	57.5	165.4
Men	Lothian	62,913	15.1	44.7	121.5
Men	Orkney	1,993	10.9	29.1	73.0
Men	Shetland	2,182	17.7	48.1	110.5
Men	Tayside	33,917	15.9	44.5	121.9
Men	Western Isles	2,432	22.0	56.2	146.5
Women	Ayrshire and Arran	35,126	11.3	34.2	91.1
Women	Borders	12,881	8.3	26.5	69.8
Women	Dumfries and Galloway	15,694	8.4	28.0	75.0
Women	Fife	32,888	9.1	27.6	73.4
Women	Forth Valley	27,258	10.3	31.4	84.7
Women	Grampian	49,934	9.7	30.6	79.7
Women	Greater Glasgow and Clyde	88,832	13.0	38.2	91.7
Women	Highland	33,412	9.2	28.7	71.6
Women	Lanarkshire	54,822	13.2	37.8	96.3
Women	Lothian	69,478	8.9	27.7	73.4
Women	Orkney	2,220	7.4	22.7	54.1
Women	Shetland	2,226	9.8	29.3	88.3
Women	Tayside	37,451	9.2	28.8	74.9
Women	Western Isles	2,641	13.9	40.0	94.1

Discussion

We have confirmed that f-Hb is higher in men than women and increases with age in both sexes and, in the greatest detail available to date, we have shown that f-Hb increases with increasing deprivation in both men and women and in all age groups.

Further, we have shown for the first time that, even in a small country, there are large variations in f-Hb in screening participants across geographical regions. These data here explain the observed differences in positivity in the SBoSP among men and women, in deprivation categories, and across NHS Boards, unsurprisingly, because positivity is a surrogate marker for f-Hb. (23)

A major strength of this study is that the number of participants studied are large. Further, the SBoSP invites individuals every two years and the data presented here are from the first 18 months of the FIT-based SBoSP, meaning that no individual will have contributed more than one f-Hb result. In addition, being based on an asymptomatic population-based screening programme, the participants fulfil the requirements of being described as reference individuals, with some caveats. Moreover, the data were generated in a single laboratory, accredited to internal standards, by with staff whose sole function is f-Hb examination. A weakness is that it has been shown that positivity and f-Hb decrease from incidence to prevalence screening rounds: our data are derived from a mixture of participants in incidence and prevalence screening rounds and the percentage of those in the incidence round is likely to be higher than previously in the FFLT because of the increase in uptake across all groups, but particularly among men, younger participants and more deprived participants. (20) A further strength is that the data on f-Hb from the FFLT, Taiwan, Florence and Barcelona were published only after peer-review. Another strength is that we were able to dissect the f-Hb distribution data for the two NHS Boards that participated in the FFLT to better examine whether the pilot evaluation provided results that informed or confounded. A weakness is that the results from the comparison studies were performed some years ago and the f-Hb distributions in Taiwan, Florence and Barcelona may have changed over time.

Brenner et al. (24) documented differences in the test performance of FIT in men and women in a screening programme and suggested some plausible reasons for the sex difference, including that colonic transit time is slower in women than in men (25), which could result in more degradation of f-Hb passed into the gut before excretion of faeces. However, this may be too simplistic, for example, constipation is more prevalent not only in females, but also with increasing age and deprivation. (26) The reasons for the increase in f-Hb with age are still unclear but may be due to increasing inherent systemic inflammation. (27) The higher f-Hb in deprivation are probably due to lifestyle factors, including higher levels of obesity, (28) sedentary lifestyles, (29) poor diets (30) and similar factors influencing the inflammatory status of the gut in the more deprived.

The differences between the results from the FIT-based SBoSP and the FFLT are striking despite using the same threshold (80 µg Hb/g faeces). The f-Hb is higher in both men and women in all age groups in the SBoSP: this explains the higher overall positivity than that found in the FFLT pilot evaluation. (19) There are several plausible reasons for the discrepancies. Firstly, the quantitative FIT system used in the SBoSP (HM-JACKarc, Hitachi Chemical Diagnostic Systems Co., Ltd, Tokyo, Japan) differs from that used in the FFLT (OC-Sensor Diana, Eiken Chemical Co., Ltd, Tokyo, Japan). Although these two FIT systems gave the same clinical outcomes in an asymptomatic screening programme, this result was achieved using the same positivity and not the same f-Hb threshold (31) exactly as in a comparison of two FIT systems performed in the Netherlands, (32) and as recommended as the strategy for comparison of FIT systems. (33) Secondly, the SBoSP data are from November 2017 to April 2019 and the FFLT data were generated from July 2010 to December 2010. Although data was obtained from the same two NHS Boards, the population demographics may have changed, particularly since the uptake in the SBoSP is higher than in the FFLT, especially among men, younger participants and, most importantly for f-Hb distributions, the more deprived. (20) Moreover, data from the pre-FIT gFOBT-based SBoSP demonstrated increasing positivity with time, indicating an increase in background occult gastrointestinal bleeding in the Scottish population (34). Thus, overall, whatever the reason for the higher f-Hb in the SBoSP than in the FFLT, the results of a pilot evaluation based on a small proportion of the intended target population should clearly be interpreted with caution. While providing high-level predictive data, such an evaluation cannot obviate the need for careful monitoring of the performance of a newly introduced screening programme and even changes to the f-Hb threshold to accommodate colonoscopy capacity may become necessary as in The Netherlands (35) and elsewhere. The means to undertake this essential monitoring have been described previously: our results support use of the advocated strategies. (23)

The data on the f-Hb distributions from the FIT-based SBoSP differ from those from the three other countries for which data in a similar format are available (6,7), confirming our previous findings that, while f-Hb is higher in men than in women in all age groups and rises with age in all countries, Scotland remains different to other countries. This implies that, since clinical outcomes depend on positivity, which is directly related to the f-Hb threshold applied, screening programme outcomes are unlikely to be directly transferrable between countries.

The question arises whether this large database should be used to create sex, age, SIMD and NHS Board partitioned reference values for f-Hb, since screening is supposedly for asymptomatic individuals and our data could be considered to represent a reference sample group. The 97.5th percentiles given in Tables 1, 2 and 4 would be the non-parametric upper reference limits of the 0.95 inter-fractile reference interval as recommended in the globally accepted Clinical Laboratory Standards Institute guideline CLSI C28-A3c. (35) The limitations of this approach have been documented in detail previously (5) and include that, although it is likely that our population does likely contain healthy individuals in the greatest number, some may be taking drugs or have colorectal conditions other than CRC, which may cause bleeding into the gut. In consequence, as previously, we consider that population-based reference intervals for f-Hb would be of very limited value.

It would be possible to use these data to set different thresholds for invitation to further investigation by sex, age, SIMD and NHS Board. However, this would be complex to initiate and execute. Further, it would be very difficult to decide on what basis such partitioned thresholds should be set. Programme positivity is the variable of greatest interest. Positivity is higher in men than women, increases with age and is higher in the more deprived, exactly as f-Hb. However, CRC is more common in men than women, in older participants and in the deprived and, in addition to significant advantages for organisation and delivery of a screening programme, use of a single f-Hb threshold does generally direct further investigation to those most likely to have colorectal neoplasia.

Since f-Hb is affected by sex, age, deprivation and geography, it might be considered that a multi-variate risk score incorporating these, and perhaps other variables, would be of value in ensuring that further investigation is offered to those that would most benefit. Clinical outcomes would be required to create a derivation cohort for development of an algorithm and studies involving validation cohorts would be required, and then prospective studies. This would seem to be complex to organise and execute in an already rolled-out successful screening programme. Further, it might be a difficult approach to explain to participants, the public, other health professionals, government and other stakeholders such as charities. In addition, f-Hb varies in different countries and seemingly with FIT system, participant characteristics and other variables, so mathematical risk scoring algorithms would be very unlikely to be transferable over geography or time.

However, it might be that a simple approach using f-Hb and expressing the participant's result as a centile of the relevant population group would have significant advantages. We have determined the distribution of f-Hb by sex, age, SIMD and NHS Board in this study. We plan now to examine the relationships between f-Hb centiles and the outcomes in the SBoSP to assess whether a simple centile-based threshold appropriate to the individual participant would lead to better screening outcomes, a precision medicine approach.

Conflict of interest statement

Authors' conflict of interest disclosure: The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CGF has undertaken paid consultancy with Hitachi Chemical Diagnostics Systems, Co., Ltd, Tokyo, Japan. Other authors have no interests to declare. Research funding played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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Ethical approval and informed consent: Neither ethical approval nor individual informed consent were required since this study used only data that were integral components of the Scottish Bowel Screening Programme.

Guarantor: CGF.

Contributors: CGF, GRCC and RJCS conceived and planned the study. GRCC generated the data and calculated the f-Hb distribution centiles. JAS is Director of the Scottish Bowel Screening Laboratory, responsible for oversight of the generation of all f-Hb results. AMcP is responsible for the day to day running of the SBoSL and the generation of the f-Hb results. JD is research fellow funded by Bowel Cancer UK, the funder of this study. CM is consultant gastroenterologist and provided expertise in the potential clinical applications of the results. RJCS is Director of the SBoSP. All authors contributed to the data analysis. All authors provided significant input to interpretation of the data and to the writing of the paper.

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Legends to Figures

Figure 1. 95th centiles of faecal haemoglobin concentration (μg Hb/g faeces) in all participants by sex and by sex and age quintile (years).

Figure 2. 95th centiles of faecal haemoglobin concentration f-Hb (μg Hb/g faeces) in men by age quintile (years) and Scottish Index of Multiple Deprivation (SIMD) quintile.

Figure 3. 95th centiles of faecal haemoglobin concentration (μg Hb/g faeces) in men by four age groups (years) in the Scottish Bowel Screening Programme (SBoSP), FIT as a first-line test (FFLT), Taiwan, Florence and Barcelona.